EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Health systems, medical products and innovation
Medical products: quality, safety, innovation

Brussels, SANTE.DDG1.D.2/MA

COMMON APPROACH

FOR DEFINITION OF REPORTABLE SERIOUS ADVERSE EVENTS AND REACTIONS (SARE) AS LAID DOWN IN THE BLOOD DIRECTIVE 2002/98/EC[1] AND COMMISSION DIRECTIVE 2005/61/EC[2]

VERSION 2024

This Common Approach document comprises recommendations for a harmonised approach for the completion of the annual web-reporting template by the competent authorities in Member States to the European Commission for Serious Adverse Reaction(s) and Event(s) associated with Blood and Blood Components - Directive 2005/61/EC and has no legally binding status for Member States.

A **Vigilance Expert Subgroup (VES)** of the Competent Authorities on Substances of Human Origin (CASoHO E01718) proposes changes and updates to the SARE reporting template and to this set of instructions. The subgroup presents and discusses its proposals with the full meetings of Competent Authorities and agrees a programmed approach for improvements with DG SANTE.

The common approach laid down here aims to facilitate comparisons between data sent to the Commission from Member States, and associated countries. The guidelines are meant to reduce the reporting burden on all parties concerned (reporting establishments, competent authorities, and the European Commission) by clarifying issues before data collection is undertaken each year.

Furthermore, due to the complexity of data collection, annual reporting of SARE has been and will continue to be a learning exercise over the coming years.

[1] Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC (OJ L 33, 8.2.2003, p. 30).
[2]Commission Directive 2005/61/EC implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events (OJ L 256,1,10, 2005, p.32).

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1. SCOPE OF REPORTING

Legal framework

EU legislation on blood states that reportable information concerns:

- "any **serious** adverse reactions (SAR) observed in recipients during or after transfusion which may be attributable to the quality and safety of blood and blood components (Directive 2005/61/EC Article 5(1))", and

- "any **serious** adverse events (SAE) which may affect the quality or safety of blood and blood components (Directive 2005/61/EC Article 6(1)."

The legal coverage of these definitions means that there is no mandated requirement to report events that do not influence the quality and safety of the blood components and reactions in recipients that are not caused by a quality or safety defect in the blood components. Similarly, reactions in donors are not reportable under this legal framework.

According to Article 168 of the consolidated version of the Treaty on the Functioning of the European Union[3], the management of healthcare, i.e., the clinical use of blood and blood components, is not a competence for the European Union, and remains under the responsibility of the Member States. SAE occurring after the start of the medical act of transfusion are, therefore, not subject to mandatory reporting under the Blood Directive. Similarly, SAR not attributable to the quality and safety of the blood or blood component are not subject to mandatory reporting under EU legislation.

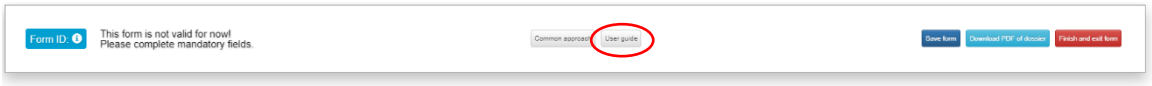
As a general principle, the Commission cannot require Member States to report more information than specified in the Blood Directives. The Commission is, however, aware that Member States would like to report additional data in some areas. In these cases, the Commission accepts and facilitates wider reporting submitted on a voluntary basis. For example, many Member States require, and consider good practice, the reporting of all **SAR in blood donors,** regardless of whether they have influenced the quality and safety of the blood components collected (see 2.1).

[3] Consolidated version of the Treaty on the Functioning of the European Union (OJ C 326, 26.10.2012, p.122-123).

1.1. Important information for completion of the electronic report

SARE data submission is performed electronically using the SANTE Data Collection Platform. The form is stored in SANTE Data Collection Platform and access to the report is limited to authorised users.

Technical instructions for the SARE web reporting form are available in the User Guide.



IMPORTANT: please make sure to **distinguish correctly** between:

- "0" - there was no activity for this reporting period for this type of blood or blood component.
- "NA" – data not available (there was activity for this type of blood or blood component, but information is not available/ partial). **"NA" does not mean Not Applicable** in the SARE reporting webform**.**

1.2. Reporting timeframe

Tables in the legally mandated format should be filled in by **reporting establishments** on an annual basis and sent to the national competent authorities. The competent authorities should then collate this information and complete the web reporting form with the aggregated data of **confirmed** cases per category over the previous year**.** The competent authorities should not forward individual forms sent by reporting establishments to the Commission.

The annual report to the European Commission aims to monitor ex-post the SAE and SAR that have occurred during the previous reporting year in the EU. Therefore, **only those SAE or SAR which occurred prior to the 31 December of the reporting year, and for which investigations are finalised and confirmed before the cut-off date for reporting to the Commission (specified by the competent authority), should be included in the annual report of that reporting year**.

SAE and SAR that occurred during the reporting year, but for which investigations are only completed after the cut-off date for reporting to the Commission, should be reported in the subsequent year during which the investigation is finalised. This will result in a certain number of cases being attributed to a wrong year, but the general trend is not expected to be significantly affected, because on average a comparable number of cases will be concerned each year. This statistical bias is therefore considered acceptable.

EXAMPLE

For the reporting year "Y", Member States *should report* to the Commission the SAE and SAR that:

- Occurred *within* the calendar year Y and for which investigations were completed and confirmation agreed on before the cut-off date for compilation of national data for reporting to the Commission (e.g., 31 March Y+1),

and

- Occurred *before* the calendar year Y but have not yet been reported to the Commission because investigations were completed - and confirmations agreed on – after the cut-off date for consolidation of the previous year(s) (e.g., 31 March Y or 31 March Y-1).

For the reporting year "Y", Member States *should not report* to the Commission the SAE and SAR that:

- Occurred during the calendar year Y, but for which investigations are still pending at the time of the cut-off date (e.g., 31 March Y+1). These cases should be reported as part of the calendar year during which the investigation is completed/final status confirmed (i.e., Y+2 or later).

1.3. Which establishments should report SARE to the competent authority?

Article 1(b) of Directive 2005/61/EC defines reporting establishments as *"the blood establishment, the hospital blood bank or facilities where the transfusion takes place that report serious adverse reactions and/or serious adverse events to the competent authority."*

Directive 2005/61/EC Article 5 on SAR and Directive 2005/61/EC Article 6 on SAE state the responsibilities of the *reporting establishments*. The responsibilities of these different establishments as regards traceability and reporting are outlined below.

1.3.1. Blood establishments

According to Directive 2002/98/EC[4]Article 3(e), a blood establishment (BE) "*shall mean any structure or body that is responsible for any aspect of the collection and testing of human blood or blood components, whatever their intended purpose, and their processing, storage, and distribution when intended for transfusion. This does not include hospital blood banks.*"

Article 1(d) of the Directive 2005/61/EC extends the responsibilities of the blood establishment to issuing blood components: *"'issue' means the provision of blood or blood components by a blood establishment or a hospital blood bank for transfusion to a recipient."*

[4] Directive 2002/98/EC of the European Parliament and of the Council setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC (OJ L 33, 8,2,2003,p.30).

1.3.2. Hospital blood banks

According to Directive 2002/98/EC Article 3(f), *"hospital blood bank shall mean a hospital unit which stores and distributes and may perform compatibility tests on blood and blood components exclusively for use within hospital facilities, including hospital-based transfusion activities."*

Similarly to BEs, hospital blood banks (HBBs) can issue blood components for transfusion (Directive 2005/61/EC Article 1(d)).

1.3.3. Facilities

Article 1(f) of Directive 2005/61/EC provides that "*'facilities' means hospitals, clinics, manufacturers, and biomedical research institutions to which blood or blood components may be delivered"*.

These facilities also have reporting obligations towards the competent authority.

1.3.3.1. Facilities where the transfusion takes place

Article 5(1) of Directive 2005/61/EC on notification of SAR requests that: *"Member States shall ensure that those facilities where transfusion occurs have procedures in place to retain the record of transfusions and to notify blood establishments without delay of any serious adverse reactions observed in recipients during or after transfusion which may be attributable to the quality or safety of blood and blood components."*

Facilities where transfusion takes place are understood as hospitals, clinics and bio-medical research institutions that perform transfusions of blood components as established therapies or clinical trials.

1.3.3.2. Facilities understood as "manufacturers of human blood/plasma derived medicinal products"

Medicinal products originating from human blood/plasma are regulated by Directive 2001/83/EC[5]. However, collection and testing of the raw blood and plasma material used for the manufacturing of these products are regulated by the Blood Directive.

SARE related to blood/plasma derived medicinal products should be reported through the national pharmacovigilance systems. However, when these SARE are linked to a problem of quality/safety that occurred during collection and/or testing, manufacturers must forward this information to the haemovigilance chain (i.e., the blood establishment that distributed the components concerned). The blood establishment should then report all SARE relating to collection and testing to the competent authority. This interdependence requires that the pharmacovigilance and haemovigilance systems are closely interconnected. It is therefore recommended that authorities on pharmacovigilance and haemovigilance communicate directly with each other.

A reaction associated with collection and testing can be captured within the associated component category. Such reactions, i.e., associated with blood /plasma material for manufacturing, should always be highlighted within the comment section of the template.

[5] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L311, 28/11/2004, p. 67).

1.4. General numbers

1.4.1. Number of reporting establishments in your country.

Article 26 of Directive 2002/98/EC requires Member States to submit to the European Commission, every 3 years, reports on the implementation of the provisions of the EU Blood Directives, including the number of reporting establishments. This question is also asked in the SARE template to ensure that this information is kept up-to-date and facilitate SARE analyses. This refers to the total number of establishments expected to report, irrespective of whether they reported data in the current exercise.

1.4.2. Percentage of completeness of data.

When data reported are partial data, competent authorities can indicate this by adding estimations of percentage of data completeness in relation to expected values for four indicators: reports received, units issued, number of recipients transfused, and number of units transfused. Thus, the percentage of reports received should be the ratio between the reports actually received and those theoretically expected. Competent authorities who know they have received all possible reports with complete data should report 100 % completeness for the four fields. If not all establishments provided information, the percentage of completeness should be calculated by counting the number of establishments which provided information and dividing this by the total number of reporting establishments for that item (entities expected to report). NB if a facility, HBB or blood establishment did not submit any SARE reports but actively confirmed that there had been no reportable cases, this entity should be included as having provided data about SARE.

1.4.3. Total number of units issued regardless of the type of component

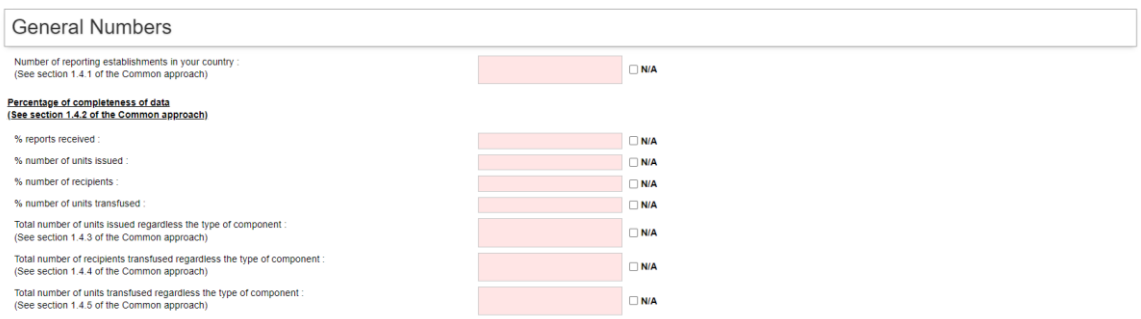
This is the total number of units issued **across** all blood components. For further information on how to report units issued please see section 2.2.1.

1.4.4. Total number of recipients transfused regardless of the type of component

This is the total number of recipients that received **any** blood components. For further information on how to report recipients, please see section 2.2.2.

1.4.5. Total number of units transfused regardless of the type of component

This is the total number of units transfused **across** all blood components. For further information on how to report units transfused please see section 2.2.3.


General Numbers

Number of reporting establishments in your country :
(See section 1.4.1 of the Common approach)
N/A

Percentage of completeness of data
(See section 1.4.2 of the Common approach)

% reports received : N/A
% number of units issued : N/A
% number of recipients : N/A
% number of units transfused : N/A
Total number of units issued regardless the type of component :
(See section 1.4.3 of the Common approach) N/A
Total number of recipients transfused regardless the type of component :
(See section 1.4.4 of the Common approach) N/A
Total number of units transfused regardless the type of component :
(See section 1.4.5 of the Common approach) N/A

2. GUIDANCE ON REPORTABLE SERIOUS ADVERSE REACTIONS (SAR)

2.1. SAR in donors

According to Article 3(h) of Directive 2002/98/EC, a SAR is *"an unintended response in donor or in patient associated with the collection or transfusion of blood or blood components that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalisation or morbidity."*

Article 5 of Directive 2005/61/EC provides a more limited definition of *reportable serious adverse reactions*, which relates to *recipients of blood and blood components.* SARs in donors are **not** reportable unless they impact on the quality and safety of the blood components.

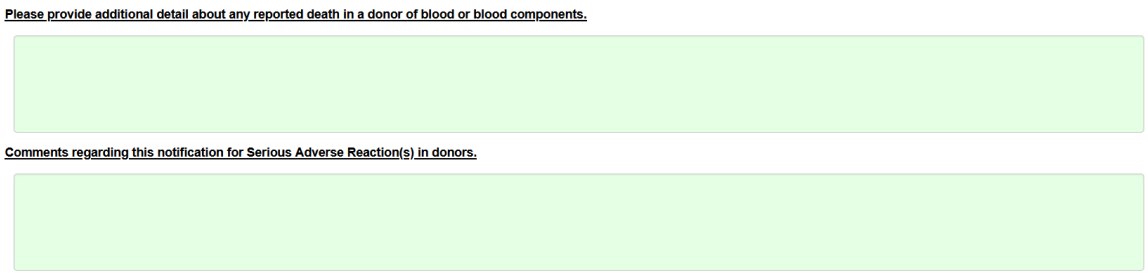
Nevertheless, most Member States collect information at a national level on SAR in donors. The Commission recognises the value of these data and invites Member States to submit an annual report concerning donor reactions on a voluntary basis. Accordingly, a specific section "SAR in donor of blood and blood components" can be found at the beginning of the SAR section of the webform. The seriousness (and therefore the reportability) of SAR in donors should be assessed using the table in section 2.3. Please refer to the ISBT-IHN-AABB[6] internationally harmonised definitions for the descriptions of the terms. An international tool[7] developed by ISBT, IHN and AABB to support severity assessment is also available and may be applied.

A table giving the most commonly reported types of SAR in donors is included in the SARE reporting webform. In general, SAR in donors should be reported if they were certainly or probably caused by the donation (imputability 2 or 3). In relation to fatalities occurring in donors, however, **all** cases of imputability 1, 2 or 3 (see imputability table in section 2.4) should be reported, i.e., where the fatality is possibly, probably, or certainly related to the donation process. Please provide the total number of fatalities along with any relevant information for each donor fatality in the comments box, such as:

(1) a brief description of type of donation and donor medical history

(2) a brief description of occurrences that led to the fatality,

(3) the conclusions (including imputability assessment) and follow-up actions (corrective and preventive), if applicable.



[6] https://www.isbtweb.org/isbt-working-parties/haemovigilance/resources.html?sortBy=featured&information_type=definitions

[7] https://www.aabb.org/docs/default-source/default-document-library/resources/severity-grading-tool-for-donor-adverse-events.pdf?sfvrsn=ff563263_4

2.2. Denominators for SAR in recipients

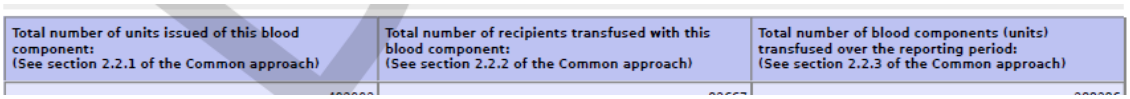
The instructions from 2.2 to 2.5 should be followed for each blood component type.

Annex II part D of Directive 2005/61/EC requires that Member States report information concerning denominators to permit detailed analysis of SAR related to blood components (for example, indicators on the number of SAR per type of blood component issued). The blood components are the following:

- Whole blood
- Red blood cells
- Platelets
- Plasma

Note that Solvent-Detergent plasma, which may be distributed by blood establishments, is a medicinal product and therefore not included here. Numbers of units distributed/transfused and SARE related to SD-plasma and other blood/plasma derived medicinal products should not be reported on this form.

Three figures are requested per type of blood component.



Total number of units issued of this blood component: (See section 2.2.1 of the Common approach)	Total number of recipients transfused with this blood component: (See section 2.2.2 of the Common approach)	Total number of blood components (units) transfused over the reporting period: (See section 2.2.3 of the Common approach)

2.2.1. Number of units issued

According to Article 1(d) of Directive 2005/61/EC, "*issue*" means the provision of blood or blood components by a BE or a HBB for transfusion to a recipient.

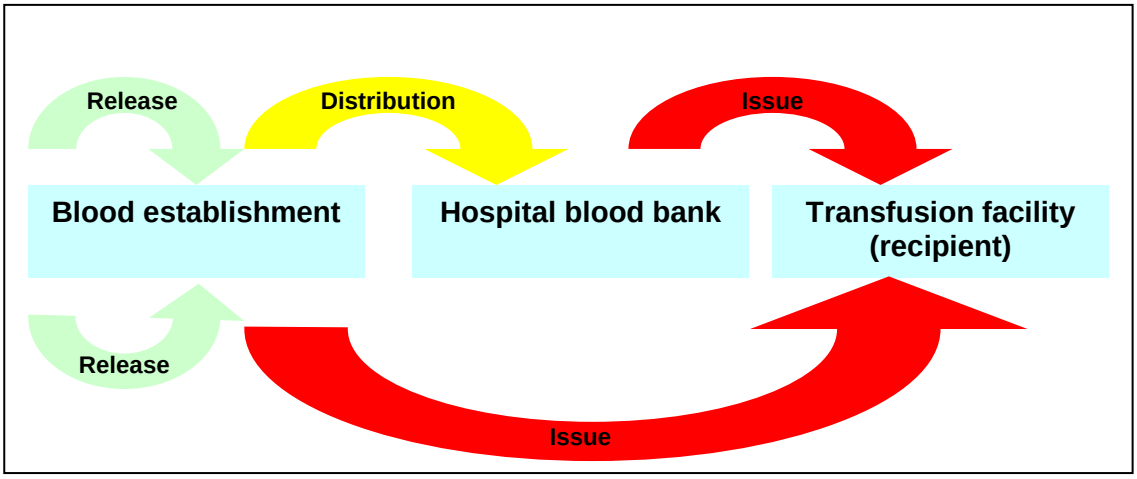
"*Issue*" differs from "*distribution*", which is *"the act of delivery of blood and blood components to other blood establishments, hospital blood banks and manufacturers of blood and plasma derived products. It does not include the issuing of blood or blood components for transfusion* (Article 3(k) of Directive 2002/98/EC)."

"*Distribution*" differs from "*release*" which means "*a process which enables a blood component to be released from a quarantine status by the use of systems and procedures to ensure that the finished product meets its release specification* (Directive 2002/98/EC Article 3(i))." A product which is *released* remains in the remit of the BE as it has not yet been *distributed*.

Therefore, a unit of blood/blood component can be *issued* by either:

- a hospital blood bank,
- a BE responsible for providing blood components for transfusion to specific recipients directly to a transfusion facility in a hospital or a clinic, or
- a BE with its own transfusion facility.

The diagram below summarises the different release/distribution/issue scenarios:



Several Member States have difficulties to obtain reliable and robust figures on issuing of blood components.

Feedback from hospital blood banks indicates that the vast majority of blood components received by them (i.e., distributed by blood establishments) are issued at least once, even if they are not actually transfused. "Units distributed" is therefore a good estimate of the "number of units issued".

For this reason, an acceptable approximation for the number of units *issued* for transfusion is the following:

Number of units issued =	Units distributed by blood establishments to the hospital blood banks + Units issued by blood establishments directly for transfusion.

Units distributed or issued several times over a one-year period should only be counted once. Handling of a unit for compatibility testing within the BE/HBB is not considered issue or distribution but should rather be considered as remaining in the inventory.

The units distributed by one BE to another BE should not be counted.

2.2.2. Number of recipients transfused

This definition is to be understood as the number of individual patients who are transfused with at least one unit of blood/blood component during the reporting year in a given country. This definition aims to aggregate the number of individual patients transfused over a year in the country, not specifying whether they received single or multiple transfusions during the period. If a recipient received more than one type of blood component in the year, they should be counted once in the total number of recipients.

If a Member State is able to link recipients to blood components, it should put these figures in the "number of recipients transfused" section of the PDF reporting template (for each individual blood component).

However, there are difficulties for the majority of Member States to conclusively link each individual recipient to a precise set of blood components (which is why this information is only optional).

A good approximation for the number of recipients transfused with a given number of blood components is:

Number of recipients transfused =	overall number of recipients transfused at least once over a one-year period, without linking these transfusion episodes to specific types of blood components.

If it is only possible to report aggregated data, as outlined in the formula above, because it is not possible to obtain recipients transfused per blood component or partial data, then this should be completed in the field "Number of recipients transfused regardless of the type of blood component" under General Numbers at the beginning of the webform.

Although this does not allow the "number of recipients/type of blood components" to be calculated, the overall number of recipients can be used as a satisfactory approximate denominator.

If it is not possible to trace patients/recipients at the national level (e.g., lack of unique national ID/reference number in the Member State), this calculation should at least be done at the hospital or clinic level. This will limit statistical bias or possible overestimations caused by some patients having several transfusion episodes in different places during a year.

If a facility cannot report a figure for the total number of recipients transfused, irrespective of whether they received one or more than one type of blood component, no figure should be counted for that facility for the overall number of recipients transfused. The numbers of transfusion recipients for the specific types of blood component should not be added up because this will be an overestimate, for instance most platelet recipients also receive red blood cells.

2.2.3. Number of units transfused

This definition is the total number of individual units transfused in hospitals/reporting establishments independently of hospitalisation episodes or patients.

Home transfusions should be included in the hospital/reporting establishment's activity.

Member States should endeavour to introduce traceability systems that facilitate the collection of information on "units transfused", as this is the 'gold-standard' denominator when analysing SAR data.

2.3. Reportable recipient SAR

Each individual adverse reaction in an individual recipient following the application of blood or blood components, and where the reaction is ‘serious’ and can be linked to the quality and safety of the blood component, should be counted as **1 adverse reaction report**. Multiple reactions in one recipient should be reported as multiple SARs.

When a SAR results from an SAE it should be reported **only** as SAR.

Reactions should be included in the number of SAR only if they were serious in nature. The following seriousness assessment table should be applied. This table is applicable both to recipient SAR and to SAR in donors (see 2.1).

NOT REPORTABLE	Insignificant	No harm to the recipient or donor
	Non-serious	Mild clinical consequences. No hospitalisation. No anticipated long-term consequence/disability.
TO BE REPORTED	**Serious**	Adverse reaction resulted in: - hospitalisation[8]or prolongation of hospitalisation and/or - persistent or significant disability or incapacity[9] and/or - intervention to preclude permanent damage or impairment of a body function and/or - evidence of transmission of a serious communicable disease
	Life-threatening [9]	- major intervention[10] to prevent death and/or - evidence of a life-threatening communicable disease
	Fatal	Death in a recipient (transfused patient) or a donor: report if you suspect that the death was an outcome of the adverse reaction. Provide relevant information in the comments box. *Recipient SAR:* Deaths that are possibly, likely/probable or certain to be attributable to the transfusion should be reported. Deaths associated with a patient's underlying conditions, or any other cause should not be included in this category. *Donor SAR:* this applies to all fatalities where a link cannot be excluded, i.e., imputability possible, probable or certain.

[8] Hospitalisation:

- Report if overnight admission to the hospital or prolongation of hospitalization was a result of the adverse reaction, even if the admission was precautionary. The criterion of hospitalisation also applies in the case of a donor.
- Emergency room visits that do not result in admission to the hospital should be evaluated for other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

[9] Disability, incapacity, or prolongation of morbidity:

- Report if the adverse reaction resulted in prolongation of morbidity or a substantial disruption of a person's ability to conduct normal life functions, i.e., the reaction resulted in persistent or significant disability or incapacity or significant disruption in the patient or donor's physical activities or quality of life.

[10] Life-threatening:

- Report if suspected that the patient or donor was at substantial risk of dying as a result of the adverse reaction or medical intervention was necessary to prevent death.
- Report major interventions including vasopressor, intubation, and transfer to intensive care.

2.4. Imputability of reportable SAR (due to the quality and safety of the blood and blood components)

Directive 2005/61/EC Article 5(3)(a) requires that *"Member States shall ensure that reporting establishments notify to the competent authority all relevant information about **serious adverse reactions of imputability level 2 or 3**, as referred to in Part B of Annex II, **attributable to the quality and safety of blood and blood components.**"*

Only reactions that are reasonably considered to have been caused by the transfused blood component, or the collection process in the case of the donor, should be included in the annual report.

Imputability levels are defined by Annex II part B of the Directive as follows*:

PART B

Serious adverse reactions — imputability levels

Imputability levels to assess serious adverse reactions.

Imputability level		Explanation
NA	Not assessable	When there is insufficient data for imputability assessment.
0	Excluded	When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to alternative causes.
	Unlikely	When the evidence is clearly in favour of attributing the adverse reaction to causes other than the blood or blood components.
1	Possible	When the evidence is indeterminate for attributing adverse reaction either to the blood or blood component or to alternative causes.
2	Likely, Probable	When the evidence is clearly in favour of attributing the adverse reaction to the blood or blood component.
3	Certain	When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to the blood or blood component.

*1. For **Donor Reactions** the imputability level is linked to the donation process, and only included if phlebotomy was started.
2. Although NA stands for not assessable in the Directive imputability tables, it only stands for Not available in the SARE reporting webform.

Article 5(3)(f) requires that reporting establishments submit a **complete report on SAR to the competent authorities on an annual basis** using the format set out in part D of Annex II of the Directive. This format requires reporting of SAR with imputability levels from Not Assessable to 3.

Article 5(3) raises questions regarding the relationship between the two sub-sections mentioned above (i.e., how to identify, and report on an annual basis, imputability with the link to quality and safety). The common approach outlined below is recommended.

The core goal of the EU legislation on blood is to set rules that guarantee a high level of quality and safety for blood components transfused within the EU. As explained previously, the Blood Directive is essential for ensuring the safety of the transfusion chain

but cannot be solely relied upon for this purpose as clinical practice lies outside of its scope due to the principle of subsidiarity.

In this context, the goals of the annual reporting of SAR to the Commission are:

(1) identifying and keeping a record of confirmed general trends on the safety of blood transfusion, which complements information gathered through other European or international sources and channels, and

(2) measuring as precisely as possible the total number of SAR during the reported year which are related to unsafe and/or bad quality blood components.

This information is crucial for identifying areas where adaptations or improvements to EU blood legislation may be required. It also enables the collection of data on the impact of quality and safety increases for blood components on the safety and efficiency of the whole transfusion chain.

It is therefore crucial to specifically identify and report those cases that are clearly part of the Blood Directive's scope as opposed to other reported SAR. For this reason, Article 5(3)(a) requires that clear-cut, confirmed SAR linked to the quality and safety of the blood component are flagged and documented specifically.

"Clear-cut" means that they meet the following two conditions:

– they are likely, probable or certain (imputability 2 to 3), and

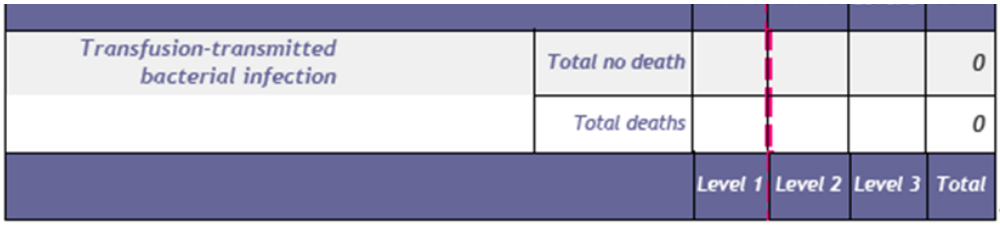
– they are attributable to a problem in quality and safety of the blood component.

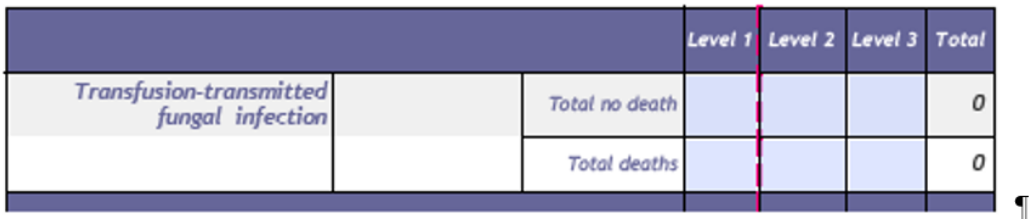
It should be noted that Member States are free to design their national reporting systems in a more stringent manner than that outlined in EU legislation (for example requiring that relevant information for all confirmed cases regardless of their imputability and/or link to quality and safety be reported).

The Commission is aware that identifying a causal link between a SAR and the quality or safety of the blood is often challenging. However, the interest in collecting data on "not assessable" and "level 0" reactions is questionable due to both its limited interest and the resources necessary for its collection. It was therefore decided that only confirmed SAR of imputability level 1 to 3 should be reported to the Commission. It was also decided that it is acceptable to exclude SAR at imputability level 1 from the report. **The annual report should therefore at least include information on the number of SAR at imputability 2 to 3 attributable to a problem in the quality and safety of the component, in line with article 5(3)(a) of Directive 2005/61/EC.**

It is currently possible to report SAR for those transfused with whole blood, red blood cells, plasma, platelets, and 'more than one component.'

For ‘more than one component’, denominators should be counted under “per component” figures. For example, if there is an allergic reaction in a patient transfused with two units of plasma and one unit of platelets, the reaction should be reported under ‘more than one component’, and the number of units transfused under the sections for plasma (two units) and platelets (one unit).





Note on the SAR tables

Total no death	Total number of confirmed reports of SAR related to transfusion of blood or blood components that did not result in the death of the recipient. The total is calculated automatically.
Total deaths	Deaths that occurred as an outcome of a SAR associated to the transfusion of blood or blood components. Deaths that are more likely to be associated with a patient's underlying conditions or any other cause should not be included in this category. In other words, only deaths that are, possibly, likely/probably or certain to be attributable to the transfusion should be reported. The total is calculated automatically.

SAR linked to transfusion-transmitted bacterial, fungal, viral, parasitic, prion and other infectious diseases with imputability 2 or 3 should be reported, as they are due to the quality and safety of the blood component.

SAR linked to SAE at the BE/HBB should be reported systematically as SAR, as they are due to quality and safety of the blood component. For instance, an error at the HBB resulting in a patient developing immunological haemolysis due to ABO incompatibility is a reportable SAR.

Multiple reactions in the same recipient, even they occurred in association with the same transfusion episode, should be reported as multiple SARs i.e. one report for each relevant category of SAR (see Annex 1 table of reportable reactions). Example: a finding of TACO and a finding of viral infection associated with a single transfusion episode should be assessed (imputability) and reported separately.

In case there is no reportable SAR for a particular component, this should be indicated in the comments box for that component. In case there are no available data for a particular component, this should also be indicated in the comments box.

Examples of comments to be added when the total # of SAR is zero.

Total number of Serious Adverse Reactions for this type of blood component

Total # of SAR no death	Total # of SAR death	Total # of SAR
0	0	0

Comments regarding this notification for Serious Adverse Reaction(s) in recipients related to whole blood.

There were not serious reactions of this type of blood component in the reporting year

or

There was no data for serious reactions of this type of blood component in the reporting year

Concerning reports where an SAR is confirmed to be fatal, any relevant information should be reported in the comments box, such as:

(1) a brief description of patient details (if possible: gender, age, initial illness, clinical indications for transfusion etc.),

(2) a brief description of the occurrences that led to the fatality,

(3) a list of transfused units of blood/blood components; for each unit, any relevant information regarding the preparation of the implicated component(s) (leucodepletion, apheresis...),

(4) the conclusions and follow-up actions (corrective and preventive), if appropriate.

2.5. Table of reportable SAR

The table in Annex I of this document provides common definitions for the SAR terms listed in the Directive 2005/61/EC Annex II part D (Annual notification format for SAR).

The International Society of Blood Transfusion (ISBT)[11] views and interpretation of haemovigilance are widely recognised in the blood transfusion community. It has therefore been agreed with ISBT, that ISBT definitions for (S)AR should be used as starting point references when available. It should be noted that these definitions may be subject to further refinement in the future, which will be reflected in later editions of this document.

Complete definitions are available in Annex I. It should be noted that this list may not cover all reportable reactions, and SAR which do not conform to the definitions should be reported under 'other'.

As yet, there are no ISBT definitions for transfusion-transmitted infections. It has been agreed that SHOT (Serious Hazard of Transfusion) definitions may be used in the meantime. Details of these definitions can be found in the table in Annex I and on the SHOT website[12].

[11] https://www.isbtweb.org/isbt-working-parties/haemovigilance/resources.html?sortBy=featured&information_type=definitions (accessed 11 March 2024)

[12] Reporting (shotuk.org) (accessed 11 March 2024) under Reporting

3. GUIDANCE ON REPORTABLE SERIOUS ADVERSE EVENTS (SAE)

3.1. Denominator: Total number of units processed

Annex III part C of Directive 2005/61/EC (Notifications of Serious Adverse Events) requires that Member States report the "total number of blood and blood components processed" prior to providing data on the occurrences of SAE.

Reporting establishment	
Reporting period	1 January-31 December *(year)*
Total number of blood and blood components processed:	

This information can be reported in the SARE web reporting form as illustrated below:

Collecting this information aims to provide a general understanding of the overall parameters of blood component processing that can be used as denominators for detailed analysis (e.g., "number of SAE per number of blood components processed").

Article 1(j) of Directive 2005/62/EC[13] on quality systems for blood establishments states that "*'processing' means any step in the preparation of a blood component that is carried out between the collection of blood and the issuing of a blood component."* According to Articles 3(e) and 3(f) of Directive 2002/98/EC, only blood establishments carry out "processing".

Activities of hospital blood banks are limited to storage, distribution, compatibility testing and issue. Hospital blood banks are not involved in the preparation of blood components, hence are not involved in "processing." This interpretation is maintained for this year's reports to the European Commission.

The number of units processed should be given as the number of individual collections performed by blood establishments. Where possible, whole blood and apheresis collections should be reported separately. Where a single collection produces two or more components, it should be counted as one collection, and therefore one unit processed.

3.2. SAEs that occur in the clinical sphere

Article 1(b) of Directive 2005/61/EC requires that blood establishments, hospital blood banks or facilities where the transfusion takes place report SAR and/or SAE to competent authorities.

According to Article 168 (7) of the TFEU[14], the clinical act of transfusion is a legal barrier beyond which the Blood Directive cannot intervene (the principle of subsidiarity). EU

[13] Commission Directive 2005/62/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards Community standards and specifications relating to a quality system for blood establishments (OJ L 256, 1.10.2005, p. 41).

[14]Consolidated version of the Treaty on the Functioning of the European Union (OJ C 326, 26.10.2012, p.123-124).Consolidated version of the Treaty establishing the European Community (OJ C 321E, 29.12.2006, p. 37).

legislation on blood applies up to the *issue* of the blood component for transfusion, after which the clinical legal sphere applies. Bedside treatment, prior to and after transfusion, is therefore the exclusive responsibility of Member States. As a result, a SAE occurring at the bedside before, during or after transfusion (e.g., the use of an infected needle) is not reportable to the Commission.

However, practical experience demonstrates that this boundary can be blurred because the two legal spheres are closely interconnected in operational terms. For example, blood components may be received by clinical staff at the hospital, and stored minutes or even hours prior to the transfusion in a fridge next to the clinical area that is monitored by the HBB. These grey zones cause uncertainty over which SAE should be reported under the Blood Directives.

Storage, even after issue to a clinical area, falls within the scope of the Blood Directive, and any SAE that occur during this time are therefore reportable. For example, a unit of blood may be stored incorrectly on a ward and then returned to the blood fridge for use at a later time, or a unit of blood may be incorrectly packaged for distribution to another hospital when a patient is transferred.

3.3. Criteria for inclusion of SAE in the annual notification

Not all adverse events are considered 'serious' (see also seriousness assessment table in section 2.3).

In the sense intended in this reporting exercise, adverse events are considered serious and reportable to the European Commission, when they may put in danger blood donors or recipients of blood or blood components, or they may have a negative impact on blood donation or on transfusion of patients.

When a SAE results in a reportable SAR in a blood recipient or donor, only the SAR, not the SAE, should be reported.

Deviations from standard operating procedures in reporting establishments, or other adverse events which have implications for the quality and safety of blood/blood components, should be reported to the Commission only when one or more of the following criteria applies:

– **<u>Inappropriate</u> blood/blood components have been <u>issued/distributed</u> for use, even if not used.**
For instance: - blood components distributed for use with incorrect blood group labels, - blood components distributed for use without the mandatory donor testing results, - blood components issued with incorrect cross-matching information, - blood components distributed for use despite a post-donation notification from the donor implying a disease transmission risk,

- blood components distributed/issued for use despite having been stored at temperatures outside the required range, - blood components issued by the HBB without specific characteristics requested by the treating physician (e.g., irradiation, CMV negative).
– **The adverse event resulted in <u>loss of any irreplaceable highly matched</u> (i.e. recipient specific) blood/blood component,**
For instance: - blood components prepared for a patient with highly specific and urgent needs lost due to a storage or processing error, - blood components of a very rare group collected for a specific recipient and lost due to a storage or processing error.
– **The adverse event resulted in the <u>loss of a significant quantity</u> of unmatched blood or blood components – a significant quantity is considered a loss that will have a negative impact (delay or cancellation) on treatment or surgery,**
For instance: - in a BE, an undetected cold-room break-down with the consequent discard of number of red cell concentrates creating a problem to respond to requests for RCC from hospitals, - a failure of the virology testing equipment results in 50% of a large blood establishment (supplying many hospitals) platelet stock expiring without being cleared for issue.
– **The adverse event could have implications for other patients or donors because of shared practices, services, supplies or donors (e.g., repeat event inside or outside the BE/HBB),**
For instance: - a defect is detected in a haemoglobin testing device known to be used by other blood establishments – no harm caused to donors due to parallel testing by a different method[15].
– **The adverse event could significantly impact the blood transfusion system (e.g., by jeopardising the confidence of blood donors or recipients).**
For instance: - confidential donor information is accidentally made publicly accessible, - donations are collected, in error, from underage donors.

[15] This should also be reported via the medical devices reporting system.

The term "near miss event"[16] is not defined in the Blood Directive but is a commonly used term. Near miss events are adverse events and, if they meet the criteria listed above, they are reportable as SAE.

SAE which are not reportable include:

- an incorrect result of compatibility testing performed by the BE/HBB due to a misidentification of the recipient's blood sample (e.g., wrong blood in tube from a clinical area and detected in the lab) is not reportable as the error falls within the "clinical practice" scope and is not covered by the Blood Directives.

- correctly cross-matched and labelled blood components that are issued by the HBB for the correct patient and transfused to the wrong patient are not reportable as the error falls within the "clinical practice" scope and is not covered by the Blood Directives.

3.4. Categorisation of SAE

Annex II of this document provides definitions of activity steps and specifications to assist with categorisation of reportable SAE (affecting the quality and safety of blood components) according to the format in Directive 2005/61/EC Annex III, part C (Annual notification format for SAE).

Activity steps
See Annex II for the list of activity steps and specifications to be selected for SAE.

It is acknowledged that more than one specification can be associated to a specific event, however for the purpose of collating data for the annual report the dominant specification should be selected. Further comments can be provided regarding other possible selections in the "additional details" box.

In case there are no reportable SAE for this reporting year, this should be indicated in the comments box for SAE. In case there no data are available for this reporting year, this should also be indicated in the comments box.

[16] According to SHOT, near miss events are "an error or deviation from standard procedures or policies that is discovered before the start of the transfusion and that could have led to a wrongful transfusion or a reaction in a recipient if transfusion was to have taken place." https://www.shotuk.org/reporting/ under SHOT definitions (accessed 11 March 2024)

4. ANNEX I: TABLE OF REPORTABLE SERIOUS ADVERSE REACTIONS

Directive 2005/61/EC categories	Reportable reactions
Immunological haemolysis due to ABO incompatibility	Acute haemolytic transfusion reaction[I] (AHTR according to ISBT) due to ABO-incompatibility
Immunological haemolysis due to other allo-antibody	Acute haemolytic transfusion reaction (AHTR according to ISBT) due to irregular antibodies Delayed haemolytic transfusion reaction[II] (DHTR according to ISBT) due to irregular antibodies
Non-immunological haemolysis	Acute haemolytic transfusion reaction (AHTR according to ISBT) due to physical, chemical or biological (but non-immune) reasons (for example mechanical stress, temperature, osmotic pressure, pH, drugs etc.)
Transfusion-transmitted bacterial infection (TTBI)	Sepsis due to TTBI[III] (according to SHOT definition of transfusion-transmitted infections)
Anaphylaxis / hypersensitivity	Severe allergic reaction[IV] (according to ISBT)
Transfusion related acute lung injury (TRALI)	TRALI[V] (according to ISBT)
Transfusion-transmitted viral infection (HBV, HCV, HIV-1/2, others)	T-t viral infection (according to SHOT definition of transfusion-transmitted infections)
Transfusion-transmitted parasitical infection (malaria, others)	T-t parasitical infection (according to SHOT definition of transfusion-transmitted infections)
Transfusion-transmitted fungal infection	T-t fungal infection (according to SHOT definition of transfusion-transmitted infections)
Post-transfusion purpura	Post transfusion purpura[VI] (PTP according to ISBT)
Graft versus host disease	Transfusion associated graft versus host disease[VII] (TA-GVHD according to ISBT)
Other serious reactions (specify)	• Febrile non haemolytic transfusion reactions[VIII] (FNHTR according to ISBT) • Severe reaction due to transfusion associated circulatory overload[IX] (TACO according to ISBT) • Severe reaction due to transfusion associated dyspnea[X] (TAD according to ISBT Definition) • Hypotensive transfusion reaction[XI] (according to ISBT) • Transfusion-transmitted prion infection • Others[XII] (including previously uncategorised complications of transfusions)

5. ANNEX II: DEFINITIONS OF ACTIVITY STEPS AND SPECIFICATIONS FOR REPORTABLE SERIOUS ADVERSE EVENTS (AFFECTING THE QUALITY AND SAFETY OF BLOOD COMPONENTS)

ACTIVITY STEPS WHERE A DEVIATION MAY OCCUR[17]

A. **Donor selection** or evaluation is performed in order to avoid collecting blood from donors with increased risk of complications and to avoid risk of transfusion-transmitted infectious diseases or other adverse reactions in the recipient (exclusive to blood establishment).

B. **Whole blood and apheresis collection** refers to the act of collection of whole blood or apheresis donations (exclusive to blood establishments).

C. **Testing** of donations refers to the act of testing blood donations in the blood establishments to meet the requirements of Directive 2002/98/EC Annex IV, as well as supplementary national requirements (exclusive to blood establishments). This includes donor testing as well as blood component testing. Compatibility testing or Cross-matching is **not** included in testing and should be reported as activity step H.

D. **Processing** is the process of transforming donations of whole blood and apheresis donations into issuable components intended for transfusion (exclusive to blood establishment). This also involves secondary processing such as irradiation.

E. **Storage** refers to the act of storing blood or blood components at blood establishments or hospital blood banks and to procedures to ensure maintenance of quality and safety from the time blood and blood components are released from a Blood Establishment and distributed to a hospital blood bank in accordance with relevant rules and written SOPs. Annex IV of Directive 2004/33/EC lays down requirements for both storage temperature and length.

F. **Distribution** is the act of delivery of blood and blood components to other blood establishments, hospital blood banks and manufacturers of blood and plasma derived products (exclusive to blood establishment). It does not include the issuing of blood or blood components for transfusion. SAE arising during issuing should be reported as activity step I.

G. **Component selection** (BE or HBB activity step) means the selection of the appropriate component by a blood establishment or hospital blood bank based on the recipient's needs. This occurs before issue.

H. **Compatibility testing/Cross-matching** (BE or HBB activity step) refers to procedures of blood group serological investigations of the intended recipient and compatibility testing with donor red cells, carried out before transfusion by a blood establishment or a hospital blood bank. This includes procedures for (electronic) compatibility verification in facilities where "Type and Screen" is used for eligible patients.

I. **Issue** (BE or HBB activity step) means the provision of blood or blood components by a blood establishment or a hospital blood bank for transfusion to recipient (Directive 2005/61/EC), i.e., the process of linking the correctly selected component to the correct patient and patient records and the labelling of that component, to maintain traceability.

J. **Other** refers to any other activity or parameter in the process that can affect the quality and safety of the component that may harm a patient.

[17] Please note that these are not legal definitions but rather aimed at facilitating reporting.

SPECIFICATIONS[18]

Component defect	**Equipment failure**	**Materials**	**System failure** - training or education - staffing, workload, or skill-mix - inadequate process, procedure, or documentation	**Human error** - incorrect decision or omission following the correct procedure - following the wrong procedure	**Other (specify)**
An SAE, meeting the criteria defined in section 3.3 of this document, should be included in the **Product Defect** category when the blood or a blood component that has been issued for use does not meet the quality and safety requirements set in annex V of the Directive 2004/33/EC due to an undetectable parameter.	An SAE, meeting the criteria defined in section 3.3 of this document, should be included in the **Equipment Failure** category when it was caused by any instruments or machinery that did not function as required at any stage from the collection to the distribution of blood and blood components. If the equipment failed because of inappropriate use, or the failure was not detected/ prevented by incorrect human action, these should be reported as human error. **Note:** Failures of medical devices, whether or not they met the criteria for SAE notification, should be reported via the medical devices reporting procedure.	An SAE, meeting the criteria in section 3.3 should be included in the **Materials** category when it was caused by any material (bags, preservation solutions, etc.) from collection to distribution of blood or blood components. If the SAE was caused by inaccurate human handling of the material, these should be reported as human error. It should be noted that medical device defects should also be reported under Medical Device legislation.	An SAE, meeting the criteria defined in section 3.3 of this document, should be included in the **System Failure** category when the quality management system fails. Insufficient training or education, high workload or -pressure, incompetent staffing or insufficient skill-mixes of staffing, inadequate processes, procedures or documentation are examples of System failure.	An SAE, meeting the criteria defined in section 3.3 of this document, should be included in the **Human error** category when it resulted from an inappropriate or undesirable human decision or behaviour that reduces, or has the potential of reducing, effectiveness, quality, safety, or system performance. SAEs should only be categorised as human error once investigation has ruled out failure of the system. Slips and lapses can be categorised as human errors.	Any SAE, meeting the criteria defined in section 3.3 of this document, should be included in the **Other** category when it cannot be classified in the already listed specifications.

[18] Please note that these are not legal definitions but rather aimed at facilitating reporting.

[I] **Acute haemolytic transfusion reaction (AHTR)** (ISBT definition)

An AHTR has its onset within 24 hours of a transfusion. Clinical or laboratory features of haemolysis are present.

Common signs of AHTR are:

- Fever
- Chills/rigors
- Facial flushing
- Chest pain
- Abdominal pain
- Back/flank pain
- Nausea/vomiting
- Diarrhoea
- Hypotension
- Pallor
- Jaundice
- Oligoanuria
- Diffuse bleeding
- Dark urine

Common laboratory features are:

- Haemoglobinemia
- Haemoglobinuria
- Decreased serum haptoglobin
- Unconjugated hyperbilirubinemia
- Increased LDH an AST levels
- Decreased haemoglobin levels

Not all clinical or laboratory features are present in cases of AHTR.
Blood group serology usually shows abnormal results but absence of immunological findings does not exclude AHTR. AHTR may also be due to erythrocyte auto-antibodies in the recipient or to non-immunological factors like mechanical factors inducing haemolysis (malfunction of a pump, of a blood warmer, use of hypotonic solutions, etc.).

[II] **Delayed haemolytic transfusion reaction (DHTR)** (ISBT definition)
DHTR usually manifests between 24 hours and 28 days after a transfusion and clinical or laboratory features of haemolysis are present. Signs and symptoms are similar to AHTR but are usually less severe. AHTR may sometimes manifests as an inadequate rise of post-transfusion haemoglobin level or unexplained fall in haemoglobin after a transfusion. Blood group serology usually shows abnormal results.

[III] **Transfusion-transmitted infection** (SHOT definition)

A report was classified as a transfusion-transmitted infection if, following investigation:

- The recipient had evidence of infection post-transfusion, and there was no evidence of infection prior to transfusion and no evidence of an alternative source of infection

and, either

- At least one component received by the infected recipient was donated by a donor who had evidence of the same transmissible infection,

or

- At least one component received by the infected recipient was shown to contain the agent of infection

Reference: Serious Hazards of Transfusions (SHOT) User Guide. Available at https://www.shotuk.org/reporting/ under SHOT definitions (accessed 11 March 2024)

[IV]**Allergic reaction** (ISBT definition)

An allergic reaction may present only with mucocutaneous signs and symptoms:

- Morbilliform rash with pruritus
- Urticaria (hives)
- Localized angioedema
- Edema of lips, tongue and uvula
- Periorbital pruritus, erythema and edema
- Conjunctival edema

occurring during or within 4 hours of transfusion. In this form it usually presents no immediate risk to life of patient and responds quickly to symptomatic treatment like anti-histamine or steroid medications. This type of allergic reaction is called 'minor allergic reaction' in many haemovigilance systems. ***For the purpose of classification this type of allergic reaction would be graded as 1, i.e. non-severe.***

An allergic reaction can also involve respiratory and/or cardiovascular systems and present like an anaphylactic reaction. There is anaphylaxis when, in addition to mucocutaneous systems there is airway compromise or severe hypotension requiring vasopressor treatment (or associated symptoms like hypotonia, syncope). The respiratory signs and symptoms may be laryngeal (tightness in the throat, dysphagia, dysphonia, hoarseness, stridor) or pulmonary (dyspnoea, cough, wheezing/bronchospasm, hypoxemia). Such a reaction usually occurs occurring during or very shortly after transfusion. ***For the purpose of classification this type of allergic reaction would be graded as 2 (severe), 3 (life-threatening) or 4 (death) depending on the course and outcome of the reaction.***

An allergic reaction classically results from the interaction of an allergen and preformed antibodies. A rise of mast cell tryptase can support the diagnosis of an allergic reaction. IgA deficiency and/or anti-IgA in the recipient has been associated with severe allergic reactions but is only one infrequent cause out of many others.

[V] **Transfusion Related Acute Lung Injury TRALI** (ISBT definition incorporating 2013 correction)

In patients with no evidence of acute lung injury (ALI) prior to transfusion, TRALI is diagnosed if a new ALI is present:

- Acute onset
- Hypoxemia
    - Pa02 / Fi02 < 300 mm Hg or
    - Oxygen saturation is < 90% on room air or
    - Other clinical evidence
- Bilateral infiltrates on frontal chest radiograph
- No evidence of left atrial hypertension (i.e. circulatory overload)
- No temporal relationship to an alternative risk factor for ALI during or within 6 hours of completion of transfusion.

Alternate risk factors for ALI are:

- Direct Lung Injury
    - Aspiration
    - Pneumonia
    - Toxic inhalation
    - Lung contusion
    - Near drowning
- Indirect Lung Injury
    - Severe sepsis
    - Shock
    - Multiple trauma
    - Burn injury
    - Acute pancreatitis
    - Cardiopulmonary bypass
    - Drug overdose

It has been suggested by the Toronto TRALI Consensus Panel to add a category of possible TRALI that would have the same definition as TRALI except for the presence of a temporal relationship to an alternative risk factor for ALI (as described above). In such a circumstance TRALI should be indicated with a possible imputability to transfusion.

TRALI is therefore a clinical syndrome and neither presence of anti-HLA or anti-HNA antibodies **in donor(s)** nor confirmation of cognate antigens **in recipient** is required for diagnosis.

[VI] **Post-transfusion purpura PTP** (ISBT definition)

PTP is characterized by thrombocytopenia arising 5-12 days following transfusion of cellular blood components with findings of antibodies in the patient directed against the Human Platelet Antigen (HPA) system.

[VII] **Transfusion Associated Graft Versus Host Disease TA-GVHD** (ISBT definition)

TA-GVHD is a clinical syndrome characterised by symptoms of fever, rash, liver dysfunction, diarrhoea, pancytopenia and findings of characteristic histological appearances on biopsy occurring 1-6 weeks following transfusion with no other apparent cause. The diagnosis of TA-GVHD is further supported by the presence of chimerism.

[VIII] **Febrile Non-haemolytic transfusion reaction FNHTR** (ISBT definition)

There is a FNHTR in the presence of one or more of:

- fever (≥38ºC oral or equivalent and a change of ≥1ºC from pretransfusion value),
- chills/rigors

This may be accompanied by headache and nausea occurring during or within four hours following transfusion without any other cause such as haemolytic transfusion reaction, bacterial contamination or underlying condition.
FNHTR could be present in absence of fever (if chills or rigors without fever).

For the purpose of international comparisons, only the most serious cases of FNHTR should be accounted for fever (≥39ºC oral or equivalent and a change of ≥2ºC from pre-transfusion value) and chills/rigors.

[IX] **Transfusion Associated Cardiovascular Overload TACO** (ISBT 2018 definition)

Patients classified with a TACO (surveillance diagnosis) should exhibit at least one required criterion* with onset during or up to 12 hours after transfusion and a total of **3 or more** criteria:

<u>* Required Criteria</u>

A. Acute or worsening respiratory compromise *and/or*
B. **Evidence of acute or worsening pulmonary oedema based on:**
   - **clinical physical examination, *and/or***
   - **radiographic chest imaging and/or other non-invasive assessment of cardiac function**

<u>Additional Criteria</u>

C. Development of cardiovascular system changes not explained by the patient's underlying medical condition, including development of tachycardia, hypertension, jugular venous distension, enlarged cardiac silhouette and/or peripheral oedema
D. **Evidence of fluid overload including any of the following: a positive fluid balance; clinical improvement following diuresis**
E. **Supportive result of a relevant biomarker, e.g., an increase of B type natriuretic peptide levels (BNP or NT-pro BNP) above the age group-specific reference range and greater than 1.5 times the pre-transfusion value.**

*A and/or B, and total of at least 3 (A to E)

[X] **Transfusion Associated TAD** (ISBT definition)

TAD is characterized by respiratory distress within 24 hours of transfusion that do not meet the criteria of TRALI, TACO, or allergic reaction. Respiratory distress should not be explained by the patient's underlying condition or any other known cause.

[XI] **Hypotensive transfusion reaction** (ISBT definition)

This reaction is characterized by hypotension defined as a drop in systolic blood pressure of ≥ 30 mm Hg occurring during or within one hour of completing transfusion **and** a systolic blood pressure ≤ 80 mm Hg. Most reactions do occur very rapidly after the start of the transfusion (within minutes).

This reaction responds rapidly to cessation of transfusion and supportive treatment. This type of reaction appears to occur more frequently in patients on ACE inhibitors. Hypotension is usually the sole manifestation, but facial flushing and gastrointestinal symptoms may occur.

All other categories of adverse reactions presenting with hypotension, especially allergic reactions, must have been excluded. The underlying condition of the patient must also have been excluded as a possible explanation for the hypotension.

[XII] **Others** (including uncommon and previously uncategorized reported complication of transfusion). Reports of new previously unreported signs and symptoms temporally related to transfusion and with no other risk factor other than transfusion e.g. like the red eye syndrome associated with some leucodepletion filters or in future if new reactions occur related to psoralene or prion filters.